PHYSIOLOGY

Edited by

ROBERT M. BERNE
MATTHEW N. LEVY

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ROBERT M. BERNE, M.D., D.Sc.(Hon.)

Chairman and Charles Slaughter Professor of Physiology,
Department of Physiology,
University of Virginia School of Medicine,
Charlottesville, Virginia

MATTHEW N. LEVY, M.D.

Chief of Investigative Medicine, Mount Sinai Medical Center;
Professor of Physiology, Medicine, and Biomedical Engineering,
Case Western Reserve University,
Cleveland, Ohio

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Contributors

MURRAY D. ALTOSE, M.D.
Associate Professor of Medicine, Case Western Reserve University; Associate Director, Department of Medicine, and Chief, Pulmonary Division, Cleveland Metropolitan General Hospital, Cleveland, Ohio

ROBERT M. BERNE, M.D., D.Sc.(Hon.)
Chairman and Charles Slaughter Professor of Physiology, Department of Physiology, University of Virginia School of Medicine, Charlottesville, Virginia

NEIL S. CHERNIACK, M.D.
Professor of Medicine, Case Western Reserve University, and Chief, Pulmonary Division, University and Cleveland VA Hospitals, Cleveland, Ohio

DAVID H. COHEN, Ph.D.
Professor and Chairman, Department of Neurobiology and Behavior, State University of New York at Stony Brook, Stony Brook, New York

BRIAN R. DULING, Ph.D.
Professor, Department of Physiology, University of Virginia School of Medicine, Charlottesville, Virginia

SAUL M. GENUTH, M.D.
Professor of Medicine, Case Western Reserve University School of Medicine, Mount Sinai Medical Center, Cleveland, Ohio

STEVEN G. KELSEN, M.D.
Associate Professor of Medicine, Case Western Reserve University, Cleveland, Ohio

HOWARD C. KUTCHAI, Ph.D.
Professor of Physiology and Director of Program in Biophysics, University of Virginia School of Medicine, Charlottesville, Virginia

MATTHEW N. LEVY, M.D.
Chief of Investigative Medicine, Mount Sinai Medical Center; Professor of Physiology, Medicine, and Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio

RICHARD A. MURPHY, Ph.D.
Professor, Department of Physiology, University of Virginia School of Medicine, Charlottesville, Virginia

OSCAR D. RATNOFF, M.D.
Professor of Medicine, Case Western Reserve University; Career Investigator of the American Heart Association; Co-Director, Division of Hematology/Oncology, Department of Medicine, University Hospitals of Cleveland, Cleveland, Ohio

S. MURRAY SHERMAN, Ph.D.
Professor, Department of Neurobiology and Behavior, State University of New York at Stony Brook, Stony Brook, New York

Preface

This textbook has been designed to emphasize broad concepts and to minimize the compilation of isolated facts. At the beginning of the book itself, as well as at the beginning of several of the sections, many of the important physicochemical principles of physiology are covered in considerable detail. When these principles could be represented profitably by equations, the bases of the equations and the major underlying assumptions have been discussed. This approach provides students with a satisfactory understanding of these basic principles, so that a mastery of certain topics will involve a minimum of pure memorization. This coverage of physicochemical principles is most evident in the cellular, cardiovascular, and respiratory sections.

In keeping with this emphasis on broad principles, homologies are grouped wherever possible. For example, in the endocrine section, discussions of the male and female gonads are included in the same chapter to highlight the similarities between the Sertoli cell functions in spermatogenesis and the granulosa cell functions in oogenesis.

Throughout the section on muscle physiology the three types of muscle are not described in sequence but are consistently considered together. It is emphasized that the basic mechanisms of contraction of skeletal, cardiac, and smooth muscles are very similar and that differences lie mainly in the relative importance of certain components of the underlying process.

In the renal physiology section, homologies again influence the presentation of material. The mechanisms whereby the kidneys handle a few important solutes are described in detail. The specific details of the transport of the myriad individual substances that pass through the kidneys are intentionally ignored.

The section on the nervous system reveals a functional neuroanatomical approach while still capturing the spirit of contemporary cellular neurophysiology. A major portion of the section is devoted to sensory and motor systems because of their relevance to clinical problems. The theoretical framework common to all sensory systems is constructed so as to facilitate the learning of the various components.

The section on hematology provides minimal coverage of blood composition. However, its emphasis on a complete and up-to-date picture of blood coagulation and its aberrations establishes a sound foundation for future clinicians.

To provide a clearer understanding of cardiovascular physiology, the entire system is initially dissected into its major components, and the functions of

these components are examined in detail. The system is then reconstructed and considered as a whole, thus indicating how the various parts interact in physiological and pathophysiological states.

In brief, the framework of this textbook comprises firmly established facts and principles. Isolated phenomena are generally ignored unless they are considered to be highly significant, and few experimental methods are described unless they are essential for the comprehension of a specific topic. Although theoretical controversies exist in virtually all areas of physiology, such controversies are not described unless they provide a deeper understanding of the subject. Thus each author has described what he believes to be the most likely mechanism responsible for the phenomenon under consideration. We have decided to make this compromise to achieve brevity, clarity, and simplicity, while recognizing that future advances might prove many of our conjectures wrong.

In keeping with our philosophy of presenting broad principles and minimizing controversies and isolated facts, we have not documented most of the assertions made throughout the book. Only a few relevant references are given at the end of each chapter. These references have been selected because they provide a current and comprehensive review of the topic, they include a clear and detailed description of important mechanisms, or they provide a complete and up-to-date bibliography of the subject.

We wish to express our appreciation to our colleagues who generously provided constructive criticism during the preparation of this book. We also want to give special thanks to Frances S. Langley, who skillfully drew the illustrations for the entire volume.

Robert M. Berne
Matthew N. Levy

Contents

SECTION I

CELLULAR PHYSIOLOGY

Howard C. Kutchai

Cellular membranes and transmembrane transport of solutes and water

Cellular membranes

Each cell is surrounded by a plasma membrane that separates it from the extracellular milieu. The plasma membrane serves as a permeability barrier that allows the cell to maintain a cytoplasmic composition far different from the composition of the extracellular fluid. The plasma membrane contains enzymes, receptors, and antigens that play central roles in the interaction of the cell with other cells and with hormones and other regulatory agents in the extracellular fluid.

The membranes that enclose the various organelles divide the cell into discrete compartments and allow the localization of particular biochemical processes in specific organelles. Many vital cellular processes take place in or on the membranes of the organelles. Striking examples are the processes of electron transport and oxidative phosphorylation, which occur on, within, and across the mitochondrial inner membrane.

Most biological membranes have certain features in common. However, in keeping with the diversity of membrane functions there are substantial differences in membrane composition and structure from one cell to another and among the membranes of a single cell.

Membrane structure

Proteins and phospholipids are the most abundant constituents of cellular membranes. A phospholipid molecule has a polar head group and two extremely nonpolar, hydrophobic fatty acyl chains. In an aqueous environment it is most energetically stable for phospholipids to form structures that allow the fatty acyl chains to be kept from contact with water. One such structure is the *lipid bilayer* (Fig. 1-1). Many phospholipids, when dispersed in water, spontaneously form lipid bilayer structures. Most of the phospholipid molecules in biological membranes have a lipid bilayer structure.

The proteins of biological membranes are associated with the membrane phospholipids in two major ways: (1) by charge interactions between the polar head groups of the phospholipids and acidic or basic amino acid residues of the protein, and (2) by hydrophobic interactions of the phospholipid acyl chains with hydrophobic amino acid residues of the proteins.

Fig. 1-2 depicts the ''fluid mosaic'' model of membrane structure. This model is consistent with many of the properties of biological membranes. Note the bilayer structure of most of the membrane phospholipids. The membrane proteins can be divided into two major classes: (1) *integral or intrinsic* membrane proteins that are embedded in the phospholipid bilayer, and (2) *peripheral or extrinsic* membrane proteins that are associated with the surface of the phospholipid bilayer. The peripheral membrane proteins interact with membrane lipids predominantly by charge interactions with the phos-

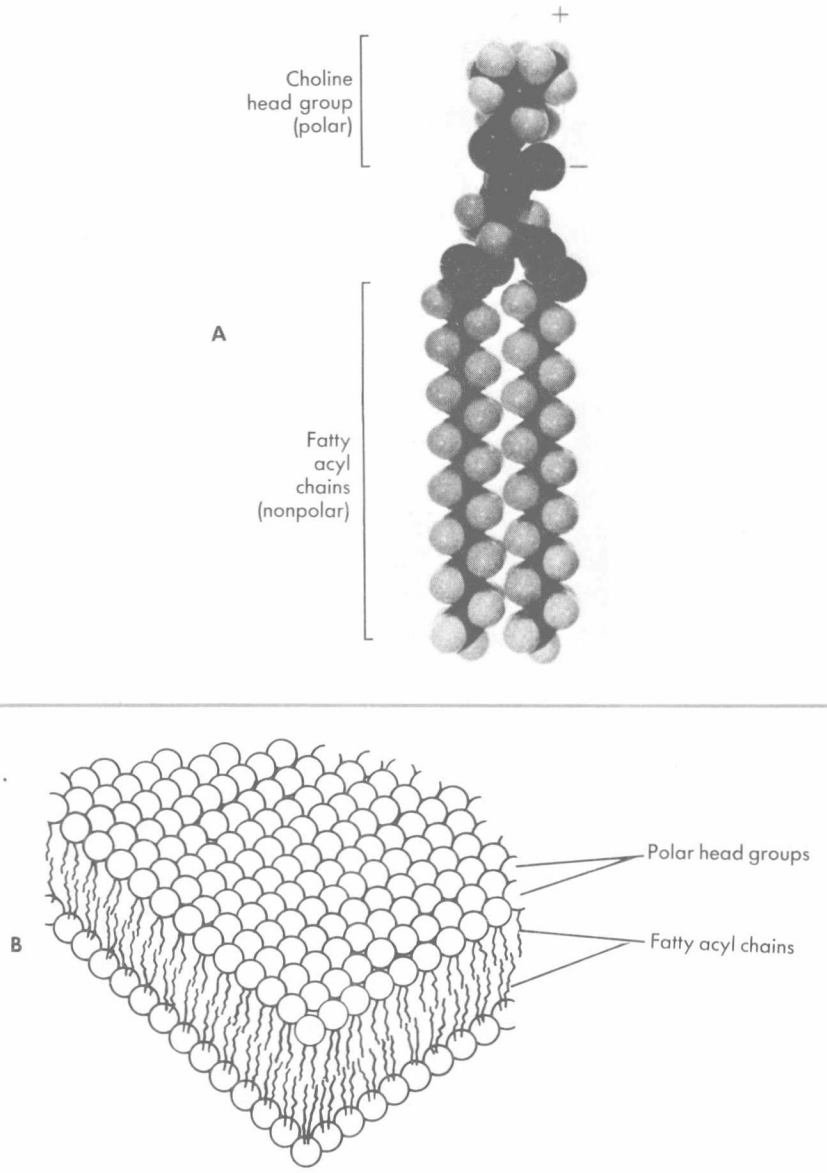

Fig. 1-1 ■ **A,** Structure of a membrane phospholipid molecule, in this case a phosphatidylcholine. **B,** Structure of a phospholipid bilayer. The open circles represent the polar head groups of the phospholipid molecules. The wavy lines represent the fatty acyl chains of the phospholipids.

pholipid polar head groups and thus sometimes may be removed from the membrane by altering the ionic composition of the medium. Integral membrane proteins have important hydrophobic interactions with the interior of the membrane. These hydrophobic interactions can be disrupted only by detergents that solubilize the integral proteins by forming their own hydrophobic interactions with nonpolar amino acid side chains.

Cellular membranes are fluid structures in which many of the constituent molecules are free to diffuse in the plane of the membrane. Most lipids and proteins are free to move in the bilayer plane, but they ''flip-flop'' from one phospholipid monolayer to the other at much slower rates. This is less likely to occur when it involves dragging a large hydrophilic moiety through the nonpolar interior of the lipid bilayer.

In some cases membrane components clearly are *not* free to diffuse in the plane of the membrane. An example of this motional constraint is the sequestration of acetylcholine receptors (integral membrane proteins) at the motor endplate of skeletal muscle. At

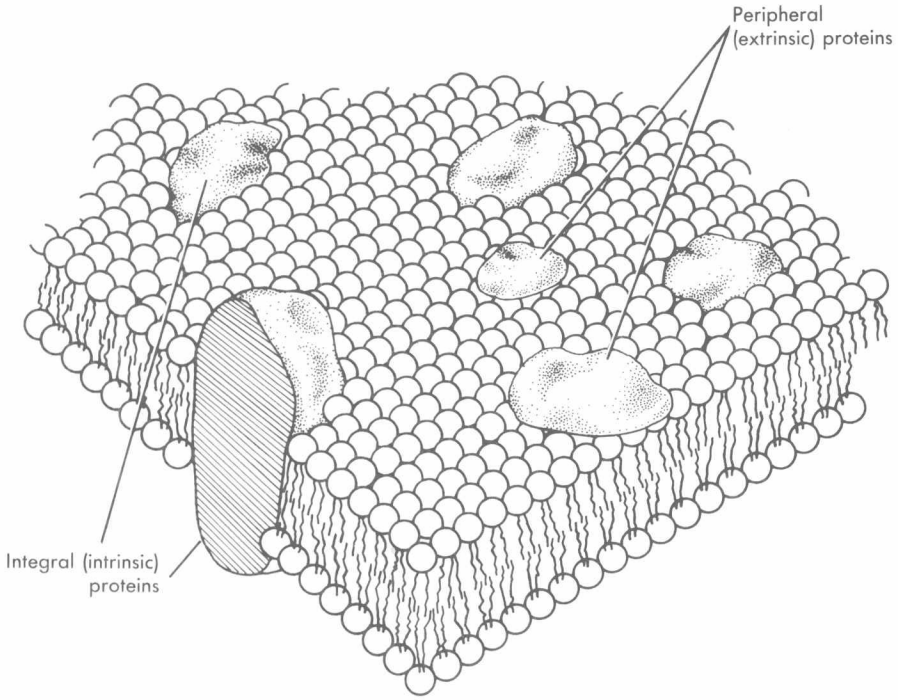

Fig. 1-2 ■ Schematic representation of the fluid mosaic model of membrane structure showing integral proteins embedded in the lipid bilayer matrix of the membrane and peripheral proteins associated with the polar head groups.

present little is known about the ways in which membrane constituents are restrained from lateral diffusion, but there is increasing evidence that the cytoskeleton may play a role in anchoring certain membrane proteins. Recent experiments suggest that specific proteins serve to link certain membrane proteins to the cytoskeleton.

■ *Membrane composition*

■ ***Lipid composition***

Major phospholipids. In animal cell membranes the most abundant phospholipids are often the choline-containing phospholipids: the lecithins (phosphatidylcholines) and the sphingomyelins. Next in abundance are usually the amino phospholipids: phosphatidylserine and phosphatidylethanolamine. Other important phospholipids that are present in smaller amounts are phosphatidylglycerol, phosphatidylinositol, and cardiolipin.

Cholesterol. Cholesterol is a major constituent of animal cell plasma membranes. The steroid nucleus of cholesterol lies parallel to the fatty acyl chains of membrane phospholipids. Thus cholesterol alters the molecular packing of the membrane phospholipids. In natural membranes cholesterol tends to diminish the lateral mobility of the lipids and proteins of the membrane.

Glycolipids. Glycolipids are present in rather small quantities, but they have important functions. Glycolipids are present mostly in plasma membranes, where their carbohydrate moieties protrude from the external surface of the membrane. The blood group antigens and certain other antigens are the carbohydrate side chains of specific glycolipids or glycoproteins.

Asymmetry of lipid distribution in the bilayer. In many membranes the lipid components are not distributed uniformly across the bilayer. As just mentioned, the glycolipids of the plasma membrane are located exclusively in the outer monolayer and thus show absolute asymmetry. Asymmetry of phospholipids occurs but is not absolute. In the red blood cell membrane, for example, the outer monolayer contains most of the

choline-containing phospholipids, whereas the inner monolayer is enriched in the amino phospholipids.

Membrane proteins

The protein composition of membranes may be simple or complex. The highly specialized membranes of the sarcoplasmic reticulum of skeletal muscle and the disks of the rod outer segment of the retina contain only a few different proteins. Plasma membranes perform many functions and may have more than 100 different protein constituents. Membrane proteins include enzymes (such as adenylate cyclase), transport proteins (such as the Na, K-ATPase), hormone receptors, receptors for neurotransmitters, and antigens.

Glycoproteins. Some membrane proteins are glycoproteins with covalently bound carbohydrate side chains. As with glycolipids, the carbohydrate chains of glycoproteins are located exclusively on the external surfaces of plasma membranes. Cell surface carbohydrate has important functions. The negative surface charge of cells is almost entirely due to the negatively charged sialic acid of glycolipids and glycoproteins. Receptors for viruses may involve surface carbohydrate. Certain surface antigenic determinants reside in carbohydrate moieties on the cell surface. Surface carbohydrate has been implicated in cellular aggregation phenomena and other forms of cell-cell interactions.

Asymmetry of membrane proteins. The absolute asymmetry of glycolipids and glycoproteins is mentioned earlier. The Na, K-ATPase of the plasma membrane and the Ca^{++} pump protein (Ca^{++}-ATPase) of the sarcoplasmic reticulum membrane are other examples of the asymmetrical functions of membrane proteins. In both cases ATP is split on the cytoplasmic face of the membrane, and some of the energy that is liberated is used to pump ions in specific directions across the membrane. In the case of the Na, K-ATPase, K^+ is pumped into the cell, and Na^+ is pumped out, whereas the Ca^{++}-ATPase actively pumps Ca^{++} into the sarcoplasmic reticulum.

It appears that most, if not all, integral membrane proteins are inserted into the membrane lipid bilayer during protein synthesis. The configuration of the protein in the membrane is the result of this specific insertion and the tertiary structure the protein assumes.

Membranes as permeability barriers

Biological membranes serve as permeability barriers. Most of the molecules present in living systems have high solubility in water and low solubility in nonpolar solvents. Such molecules have low solubility in the nonpolar environment in the interior of the lipid bilayer of biological membranes. As a consequence, biological membranes pose a formidable permeability barrier to most water-soluble molecules. The plasma membrane is a permeability barrier between the cytoplasm and the extracellular fluid. This permeability barrier allows the maintenance of cytoplasmic concentrations of many substances that differ greatly from their concentrations in the extracellular fluid. The localization of various cellular processes in certain organelles depends on the barrier properties of cellular membranes. For example, the inner mitochondrial membrane is impermeable to the enzymes of the tricarboxylic acid cycle, allowing the localization of these enzymes in the mitochondrial matrix. The spatial organization of chemical and physical processes in the cell depends on the barrier functions of cellular membranes.

The passage of important molecules across membranes at controlled rates plays a central role in the life of the cell. Examples are the uptake of nutrient molecules, the discharge of waste products, and the release of secreted molecules.

In some cases molecules move from one side of a membrane to another without actually moving through the membrane itself. Endocytosis and exocytosis are examples of processes that transfer molecules across, but not through, biological membranes. In other cases molecules cross a particular membrane by actually moving *through* the membrane by passing through or between the molecules that make up the membrane.

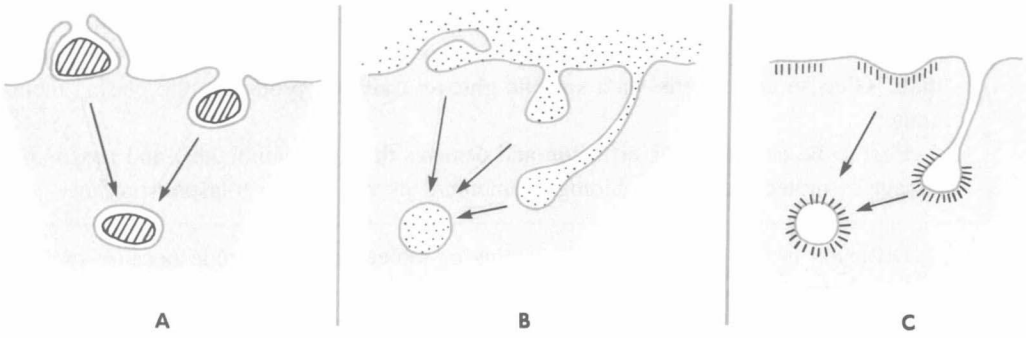

Fig. 1-3 ■ Schematic depiction of endocytotic processes. **A,** Phagocytosis of a solid particle. **B,** Pinocytosis of extracellular fluid. **C,** Receptor-mediated endocytosis by coated pits. (Redrawn from Silverstein, S.C., et al.: Ann. Rev. Biochem. **46:**669, 1977. Reproduced, with permission, from the Annual Review of Biochemistry. © 1977 by Annual Reviews Inc.)

■ *Transport across, but not through, membranes*

Endocytosis. Endocytosis allows material to enter the cell without passing through the membrane (Fig. 1-3). When particulate material is taken up, the process is termed *phagocytosis* (Fig. 1-3, *A*). When soluble molecules are taken up, it is called *pinocytosis* (Fig. 1-3, *B*). Sometimes special regions of the plasma membrane, whose cytoplasmic surface is covered with bristles made primarily of a protein called *clathrin,* are involved in endocytosis. These bristle-covered regions are called *coated pits,* and their endocytosis gives rise to *coated vesicles* (Fig. 1-3, *C*). The coated pits appear to be involved primarily in *receptor-mediated endocytosis*. Specific proteins to be taken up are recognized and bound by specific membrane receptor proteins in the coated pits. The binding often leads to aggregation of receptor-ligand complexes, and the binding appears to trigger endocytosis in ways that are not yet understood. Endocytosis is an active process that requires metabolic energy. Endocytosis also can occur in regions of the plasma membrane that do not contain coated pits.

Exocytosis. Molecules can be ejected from cells by exocytosis, a process that resembles endocytosis in reverse. The release of neurotransmitters, which is considered in more detail in Chapter 4, takes place by exocytosis. Exocytosis is responsible for the release of secretory proteins by many cells; the release of pancreatic zymogens from the acinar cells of the pancreas is a well-studied example. In such cases the proteins to be secreted are stored in secretory vesicles in the cytoplasm. A stimulus to secrete causes fusion of the secretory vesicles with the plasma membrane and release of the vesicle contents by exocytosis.

Fusion of membrane vesicles. The contents of one type of organelle can be transferred to another organelle by fusion of the membranes of the organelles. In some cells secretory products are transferred from the endoplasmic reticulum to the Golgi apparatus by fusion of endoplasmic reticulum vesicles containing the secretory protein with membranous sacs of the Golgi apparatus. Membrane fusion also occurs between phagocytic vesicles and lysosomes and allows intracellular digestion of phagocytosed material to proceed.

■ *Transport of molecules through biological membranes*

The traffic of molecules through biological membranes is vital for most cellular processes. Some molecules move through biological membranes simply by diffusing among the molecules that make up the membrane, whereas the passage of other molecules involves the mediation of *specific transport proteins* in the membrane.

Oxygen, for example, is a small molecule with fair solubility in nonpolar solvents.